

**COMBINED INTERFERON ALFA AND LIPSOSMAL-ENCAPSULATED
ALL-TRANS RETINOIC ACID, INCLUDING PREPARATION AND USE**

Cross-Reference to related Applications

5 This application claims priority to Provisional Application
60/193,565 filed March 31, 2000.

Field of the Invention

Alfa interferon (α -IFN or alpha-interferon) and liposomal all-trans
retinoic acid is useful in cancer treatment with particular reference to renal
10 cancer. Optionally, a regimen of α -interferon from about 3 to about 5 million
units sc daily and liposomal all-trans retinoic acid (*e.g.*, ATRAGEN[®], Aronex
Pharmaceuticals, The Woodlands, TX) at a dose from about 15 mg/m² to
about 90mg/m², or about 140mg/m², or about 300mg/m² or more. Dosage
periodicity of about five times per week for both drugs in about 8 week
15 cycles is useful. In some instances interferon is dosed more often including
every other day and daily.

Background of the Invention

The incidence of renal cell carcinoma is estimated to be approximately
20 30,000 new cases annually, with a death rate of 10,000 patients per year
(1). At the time of diagnosis approximately fifty percent of patients have
disease localized to the kidney, thirty percent of patients have distant
metastases, and the remaining twenty percent of patients have locally
advanced disease (2). Currently, surgical resection of all discernible disease
25 is the only potentially curative therapy. For patients with stage I or II

disease, the five year survival ranges from 45 to 85%, while for patients with stage III disease the five year survival ranges from 15 to 35% (2).

Occasionally, selected patients with stage IV disease have prolonged disease free survival after resection of solitary metastases.

5 For those patients with surgically unresectable disease, therapeutic options include chemotherapy, hormonal therapy and immunotherapy. Unfortunately, all of these therapies are relatively unsuccessful. Hormonal therapy has little or no therapeutic effect (3). Similarly, available chemotherapy has been generally ineffective. More than 40 drugs have been
10 investigated, but none achieved a response proportion greater than 15-20% alone or in combination (4). The potential therapeutic benefit of biologic response modifiers like interferons (IFN) have been studied in RCC (5). Queseda, et al, first reported the clinical efficacy of human leukocyte IFN in metastatic RCC (6). Subsequently, numerous clinical trials with various
15 subtypes of IFN including purified human lymphoblastoid interferon-alpha and purified recombinant interferon-alpha 2a and 2b have been performed. In these trials, the proportion of patients experiencing major responses is only about 15% (and a range of 5-29%), with a median duration of response ranging from three to 16 months (5; 7). In a review of 18 trials of renal
20 carcinoma treated with interferon-alpha, Krown et al found no significant difference in response based on type or schedule of drug (7). There was, however, evidence that moderate doses of interferon-alpha produced superior response rates when compared to either low or high doses. Thus,

the overwhelming majority of patients with RCC are unresponsive to the antitumor effects of IFN given as a single agent (8; 9).

Other clinical trials have investigated the efficacy of other biological response modifiers alone or in combination with IFN α in the treatment of patients with metastatic RCC (10; 11). Interleukin-2 (IL-2), with or without lymphokine-activated killer (LAK) cells, has been extensively studied. Although initial clinical trials reported significant numbers of major clinical responses with IL-2, this was associated with significant toxicity and few patients have shown long term clinical benefit (12; 13). The addition of interleukin-2 (IL-2) to IFN resulted in a higher number of clinical responses in patients with advanced RCC in one study (14), however, this was not observed in subsequent trials (15; 16). Overall, the data suggest that, similar to IFN α , the proportion of patients experiencing significant responses with IL-2 based therapy is approximately 15% (17). It is clear that the need exists for more effective therapy for patients with advanced renal cancer.

A phase II trial of Interferon alfa-2a and free (non-liposomal) 13-cis-retinoic acid (CRA) was conducted at Memorial Sloan-Kettering Cancer Center (MSKCC) in patients with advanced renal cell carcinoma (RCC). IFN was given daily; starting at 3 million units (MU) and the dose was escalated every seven days from 3 to 6 to 9 MU. The CRA was given daily at a dose of 1mg/kg/day. Thirteen (30%) of 43 evaluable patients achieved a major response (three complete, ten partial) (34). In addition to lung and nodal metastases, responding sites included bone metastases and renal primary

tumors.

Other trials have also reported using a combination of 13-cis retinoic acid and IFN (36; 37). In one study examining the pharmacokinetics of free all-trans retinoic acid (ATRA) in patients with renal cancer concomitantly
 5 treated with IFN, peak levels of atra in the serum declined after three months on therapy (38).

Summary of the Invention

This invention comprises a method of inhibiting the growth of cancer
 10 cells , and particularly renal cancer cells, comprising exposing cancerous cells to a therapeutically effective amount of a composition which comprises at least one interferon and a retinoid, wherein said retinoid is associated with lipid carrier particles. Particular note is made of the method the retinoid is retinoic acid; such as all-trans retinoic acid.

15 In some embodiments of the method the lipid carrier particles comprise all-trans retinoic acid, lipid, and a triglyceride and the molar ratio of retinoid to lipid is at least about 15:85, where the triglyceride is at least about 15% by weight of the composition, and where the composition is stable in an aqueous environment. In specific embodiment the method of
 20 comprises administering said retinoid composition in doses administered over a period of at least one-half hour, and, optionally, administering said retinoid composition at a frequency of about every other day or less frequent.

In another embodiment this invention comprises a method of inhibiting

the growth of cancer cells comprising exposing cancerous cells to a therapeutically effective amount of a composition which comprises at least one interferon and further co-timely exposing of said cancerous cells to a therapeutically effective amount of a retinoid, wherein said retinoid is

5 associated with lipid carrier particles.

A composition of the present invention comprises a therapeutic treatment kit for the treatment of cancer comprising interferon, retinoid and instructional materials for the combined use of said retinoid and interferon. In some instances instructional materials include such information as dosage,

10 indication, and contraindication and storage parameters.

Detailed Description of the Invention

A. "Exposing" as used in relation to cancerous cells shall mean *in vivo* and further include *extra corporeal* as well as *in vitro* applications. *In vitro* applications are particularly useful in diagnostic and screening

15 applications of the present invention.

B. Cancer shall be broadly understood to mean an abnormal uncontrolled growth of tissue that has potential to spread to distant sites of the body. In particular, cancer shall include renal cell carcinoma including

20 chromophobe cell renal carcinoma and further granular/eosinophilic variants of these tumors and renal oncocytoma, renal leiomyosarcoma. Particular note is made of head, neck, and breast cancer. Head, neck, and breast cancer are often found to have reduced retinoid levels. In specific instances

tumor cells presenting with low retinoid levels exhibit enhanced therapeutic response to the instant therapy.

C. "Therapeutically effective amount" is defined independently for each drug. As to L-ATRA a therapeutically effective amount shall mean
5 about 15-300 mg/m² and particularly 90 mg/m².

As to interferon alfa a therapeutically effective amount shall mean from about 1 to about 25 million IU and particularly 3-5 million IU.

It is anticipated that interferons alfa, beta, gamma, and omega are administered in similar doses. Doses are generally adjusted to at or below
10 the maximum tolerated dose (MTD). Signs indicative of interferon toxicity are noted to be as to hematologic toxicity, anemia, thrombocytopenia, leukopenia; as to gastrointestinal toxicity, diarrhea, dyspepsia, dysphagia, N/V, abdominal pain; as to liver toxicity increases in bilirubin, alk phos and LFTs; as to kidney and bladder, microscopic hematuria, pyuria, azotemia,
15 proteinuria, acute renal failure, nephrotic syndrome, glycosuria, albuminuria; as to pulmonary, orthopnea, dyspnea, bronchospasm, coughing, pulmonary edema, ARDS; as to cardiac toxicity syncope, MI, SVT, bradycardia, tachycardia, dizziness, hyptoension, hypertension. Neurological toxicity are confusion, tremors, numbness, paresthesia, inability to concentrate,
20 somnolence, hallucinations, encephalopathy, seizure, coma, psychomotor retardation, memory dysfunction, dry mouth, sweating, personality disorder, agitation, neuropathy, depression, anxiety, aphasia, retinal infarction with vision loss, eye pain, hemianopsis, taste change, headache, syncope,

insomnia. Dermal toxicity of skin rash, urticaria, epidermal necrosis, maculopapular rash is noted. Metabolic toxicity manifests as hyperglycemia. In addition coagulation is monitored for increase in PT/PTT. Also the presence of pharyngitis, alopecia, fatigue, malaise, anorexia, weight loss, fever, chills, myalgia, arthralgia, cyanosis are potential toxic responses to interferon.

Liposomal ATRA at toxic doses displays hematologic thrombocytopenia. In addition gastrointestinal toxicity of N/V and mucositis. Liver toxicity increase alk phos and LDH. Neurologic toxicity results in emotional changes, and headache. Dermal toxicity is noted in dry skin, dermatitis. Also, metabolic changes are found in an increase in triglycerides levels in the blood. Toxicity is also determined by alopecia, anorexia, dry eyes, cheilitis, epistaxis, joint pain, fatigue, pruritus, and conjunctivitis.

The foregoing notwithstanding, a supervising clinician will understand that initial myelosuppression is a favorable sign in the treatment of leukemias.

Without being bound by any particular theory it is believed that retinoid effects are mediated through retinoic acid nuclear receptors (RARs) which are members of the steroid receptor superfamily of ligand-dependent transcriptional factors (25). Two distinct retinoid nuclear receptor systems exist, the RARs (RAR-a, -b, -g) and the RXRs (RXR-a, -b, -g) (26). The RARs and RXRs can heterodimerize following RA binding, and transcriptionally activate or repress other genes which mediate the growth and differentiation effects of RA (26; 27).

D. "Interferon" shall be broadly understood to mean any of several glycoproteins that help the body fight off viral infections. Particular note is made of interferons alfa (or alpha), beta, and gamma. Interferon alpha is the main type of interferon produced by the white blood cells

5 Particular reference is made to interferon alfa-2b, recombinant, (Intron A, Schering) , and interferon alfa 2a (Roferon, Hofman LaRoche).

E. "Retinoid" shall be broadly understood to mean the natural and synthetic derivatives of vitamin A. Isotretinoin (13 cis-retinoic acid) and tretinoin (all trans retinoic acid) represent the two naturally occurring isomers
10 of retinoic acid (18).

F. Lipid Carrier particle shall be expansively understood to mean all lipid-drug particulates. Reference also is made to US 5,811,119, "Formulation and Use of Carotenoids in Treatment of Cancer" to Mehta et al. Reference is further made to U.S. Pat. 4,610,868 to Fountain. Fountain is a
15 patent which describes amorphous lipid particles, with particular reference to Fountain col. 7, lines 1-17. Lipid carrier particles is a term known in the art defining structures in addition to liposomes.

Particular reference is made to liposomal ATRA. In one embodiment. Liposomal ATRA or liposomal tretinoin (also known as liposomal ATRA
20 Tretinoin^{LF} or ATRAGEN[®]) is provide by Aronex Pharmaceuticals, Inc (The Woodlands, Texas). Without being bound by any particular theory, the liposomal delivery system improves the activity of the tretinoin by altering its pharmacological profile, such as changing the drug's pharmacokinetics and

tissue distribution. Once injected into the bloodstream, liposomes are quickly cleared by the reticuloendothelial system (RES) cells which include the liver and spleen and, most importantly, the hematopoietic tissues from which the malignant cells are seeded. Minimal liposomal uptake occurs in
5 tissues with continuous, non-fenestrated capillaries such as muscle and nervous tissue.

Another beneficial difference is that the lipid formulation bypasses the clearance mechanism that evolves in the livers of patients treated with the oral formulation. In addition, toxicities associated with oral doses of
10 tretinoin are reduced in some cases because liposome encapsulation of tretinoin decreases direct exposure of the tretinoin during circulation to levels below the orally administered toxic dose. The latter allows greater total exposure of the drug on initial dose accompanied by slower clearance of the tretinoin. This is also understood to be an avoidance of ATRA resistance.

15 G. "Co-timely" as to drug administration shall mean administration of interferon while L-ATRA is present in a therapeutically effective amount or the reverse. It is to be understood that in some instances this will require sequential administration. In some instances, multiple routes of administration will be employed such as intravenous or subcutaneous
20 injection of an alfa interferon, while a L-ATRA is administered i.v. prior to or subsequent to such interferon administration.

Treatment is usefully employs liposomal ATRA in the form of ATRAGEN®. A vial of lyophilized ATRAGEN® is reconstituted with 50 ml of

0.9% sodium chloride for injection, USP, to provide a 2 mg per ml of liposomal suspension requiring no further dilution steps. The vial is then shaken vigorously for one minute. This forms a dispersion of ATRAGEN® liposomes. Several minutes is then for the foaming of reconstituted product to subside prior to transfer of the suspension. Due to the foaming of the reconstituted product, approximately 5-10 mL of the 50 mL of product may not be transferable. At this point, the reconstituted drug is aseptically transferred into an I.V. bag or bottle. Alternatively, properly cover the I.V. bag or bottle to sufficiently reduce light exposure during infusion (I. V. lines do not generally require coverage. As to interferon-alfa 2b, Inton A, (Schering Oncology)., this is available as a reconstituted solution for injection in 3, 5 and 10 million IU vials. Each vial contains 3 (or 5 or 10) million IU of Interferon alfa-2b; recombinant, dissolved in 0.5 ml (3 and 5 million unit vials) or 1 ml (10 million unit vials). Each 1ml contains 7.5 mg sodium chloride, 1.8 mg sodium phosphate dibasic, 1.3 mg sodium phosphate monobasic, 0.1 mg edetate disodium, 0.1 mg polysorbate 80, and 1.5 mg m-cresol as preservative. Vials are stored in refrigerator (4° C) prior to use and is stable for up to 7 days at 35°C and at 30°C for up to 14 days.

In some instances, interferon is administered s.c. Blood levels tend to peak at about 4 hours. For patient comfort, interferon is usefully administered in the evening so that a subject will be asleep during the more severe side-effects. Co-timely administration particular is noted to present ATRAGEN® concentrations to coincide with interferon peaks. In one

embodiment, interferon is administered Monday through Friday and ATRAGEN® Monday, Wednesday and Friday.

Example 1

A 63 year old human male presented with metastatic renal cancer. Alfa
5 interferon and ATRAGEN® were administered as follows:

Interferon at 5×10^6 units s.c. daily Monday through Friday, and ATRAGEN®
15mg/m² i.v., Monday, Wednesday and Friday.

This treatment was provided in 8 week cycles resulting in regression of the
cancer.

10 Relevant additional information is available in the following:

1. Parker, S.L., Tong, T., Bolden, S., and Wingo, P.A. Cancer statistics, 1997. CA - Cancer J Clin, 47: 5-27, 1997.
2. Motzer, R.J., Bander, N.H., and Nanus, D.M. Renal-cell carcinoma. N.Engl.J.Med., 335: 865-875, 1996.
- 15 3. Yagoda, A., Petrylak, D., and Thompson, S. Cytotoxic chemotherapy for advanced renal cell carcinoma. [Review]. Urologic Clinics of North America, 20: 303-321, 1993.
4. Motzer, R.J. and Vogelzang, N.J. Chemotherapy for renal cell carcinoma. In: D. Raghavan, H.I. Scher, S.A. Leibel and P. Lange (eds.),
20 Principles and practice of genitourinary oncology, pp. 885-896, Philadelphia: Lippincott-Raven Publishers. 1997.
5. Buzaid, A.C. and Todd, M.B. Therapeutic options in renal cell carcinoma. Semin.Oncol., 16: 12-19, 1989.

6. Quesada, J.R., Swanson, D.A., Trindade, A., and Gutterman, J.U.
Renal cell carcinoma: antitumor effects of leukocyte interferon. *Cancer Res.*,
43: 940-947, 1983.
7. Krown, S.E. Interferon treatment of Renal Cell Carcinoma. *Cancer*,
5 59: 647-651, 1987.
8. Quesada, J.R. Role of interferons in the therapy of metastatic renal
cell carcinoma. *Urology*, 34: 80-83, 1989.
9. Horoszewicz, J.S. and Murphy, G.P. An assessment of the current
use of human interferons in therapy of urological cancers. *Urology*, 142:
10 1173-1180, 1989.
10. Quesada, J.R. Biologic Response Modifiers in the Therapy of
Metastatic Renal Cell Carcinoma. *Seminars in Oncology*, 15: 396-407,
1988.
11. Haas, G.P., Hillman, G.G., Redman, B.G., and Pontes, J.E.
15 Immunotherapy of renal cell carcinoma. *CA-A Cancer J.Clinicians*, 43: 177-
187, 1993.
12. Kragel, A.H., Travis, W.D., Steis, R.G., Rosenberg, S.A., and
Roberts, W.C. Myocarditis or acute myocardial infarction associated with
interleukin-2 therapy for cancer. *Cancer*, 66: 1513-1516, 1990.
- 20 13. Rosenberg, S.A. Immunotherapy and gene therapy of cancer.
Cancer Res., 51: 5074s-5079s, 1991.
14. Figlin, R.A., Belldegrun, A., Moldawer, N., Zeffren, J., and
desertion, J. Concomittant administration of recombinant human interleukin-

2 and recombinant interferon alfa-2a: An active outpatient regimen in metastatic renal cell carcinoma. *J Clin Oncol.*, 10: 414-421, 1992.

15 15. Ilion, D.H., Motzer, R.J., Creation, R.G., Vogelzang, N.J., Bajorin, D.F., Scher, H.I., Nanus, D., O'Moore, P., Marathias, K., and Bosl, G.J. A phase II trial of interleukin-2 and interferon alfa-2a in patients with advanced renal cell carcinoma. *J Clin Oncol.*, 10: 1124-1130, 1992.

16. Atkins, M.B., Sparano, J., Fisher, R.I., Weiss, G.R., Margolin, K.A., Fink, K.I., Rubinstein, L., Louie, A., Mier, J.W., Gucalp, R., Sosman, J.A., Boldt, D.H., Doroshow, J.H., Aronson, F.R., and Sznol, M. Randomized
10 phase II trial of high-dose interleukin-2 either alone or in combination with interferon alfa-2b in advanced renal cell carcinoma. *J Clin Oncol.*, 11: 661-670, 1993.

17. Wirth, M.P. Immunotherapy for metastatic renal cell carcinoma. *Urol.Clin.North.Am.*, 20: 283-295, 1993.

15 18. Lippman, S.M. and Meyskens, F.L.Jr. Vitamin A derivatives in the prevention and treatment of human cancer. *J.Am.Coll.Nutr.*, 7: 269-284, 1988.

19. Smith, M.A., Parkinson, D.P., Cheson, B.D., and Friedman, M.A. Retinoids in cancer therapy. *J Clin.Oncol.*, 10: 839-864, 1992.

20 20. Lippman, S.M. and Meyskens, F.L., Jr. Results of the use of vitamin A and retinoids in cutaneous malignancies. *Pharmacol.Ther.*, 40: 107-122, 1989.

21. Kraemer, K.H., Di-Giovanna, J.J., Moshell, A.N., Tarone, R.E., and

Peck, G.L. Prevention of skin cancer in xeroderma pigmentosum with the use of oral isotretinoin. *N Engl.J.Med.*, 318: 1633-1637, 1988.

22. Hong, W.K., Endicott, J., and Itri, L.M. 13-cis-retinoic acid in the treatment of oral leukoplakia. *N.Eng.J.Med.*, 315: 1501-1505, 1986.

5 23. Frankel, S.R., Eardley, A., Heller, G., Berman, E., Miller, W.H., Jr., Dmitrovsky, E, and Warrell, R.P., Jr. All-trans retinoic acid for acute promyelocytic leukemia. Results of the New York Study. *Ann.Intern.Med.*, 120: 278-286, 1994.

24. Muindi, J., Frankel, S.R., Miller, W.H., Jr., Jakubowski, A.,
10 Scheinberg, D.A., Young, C.W., Dmitrovsky, E., and Warrell, R.P., Jr. Continuous treatment with all-trans retinoic acid causes a progressive reduction in plasma drug concentrations: implications for relapse and retinoid "resistance" in patients with acute promyelocytic leukemia [published erratum appears in *Blood* 1992 Aug 1;80(3):855]. *Blood*, 79: 299-303,
15 1992.

25. Evans, R. The steroid and thyroid hormone receptor superfamily. *Science*, 240: 889-895, 1988.

26. Pemrick, S.M., Lucas, D.A., and Grippo, J.F. The retinoid receptors. [Review]. *Leukemia*, 8 Suppl 3: S1-10, 1994.

20 27. Chambon, P. The retinoid signaling pathway: molecular and genetic analyses. [Review]. *Semin.Cell Biol*, 5: 115-125, 1994.

28. Marth, C., Daxenbichler, G., and Dapunt, O. Synergistic antiproliferative effect of human recombinant interferons and retinoic acid in

cultured breast cancer cells. *J.Natl.Cancer Inst.*, 77: 1197-1197, 1986.

29. Frey, J.R., Peck, R., and Bollag, W. Antiproliferative activity of retinoids, interferon alpha and their combination in five human transformed cell lines. *Cancer Letters*, 57: 223-227, 1991.

5 30. Bollag, W. and Peck, R. Modulation of growth and differentiation by combined retinoids and cytokines in cancer. In: W.K. Hong and R. Lotan (eds.), *Retinoids in oncology*, pp. 89-108, New York: Marcel Dekker, Inc. 1993.

31. Arbaje, Y.M., Bittner, G., Yingling, J.M., Storer, B., and Schiller, 10 J.H. Antiproliferative effects of interferons alpha and beta in combination with 5-fluorouracil, cisplatin, and cis- and trans-retinoic acid in three human lung carcinoma cell lines. *J Interferon Res*, 13 : 25-32, 1993.

32. Lippman, S.M., Parkinson, D.R., Itri, L.M., Weber, R.S., Schantz, S.P., Ota, D.M., Schusterman, M.A., Krakoff, I.H., Gutterman, J.U.; and 15 Hong, W.K. 13-cis-retinoic acid and interferon alpha-2a: effective combination therapy for advanced squamous cell carcinoma of the skin. *J.Natl.Cancer Inst.*, 84: 235-241, 1992.

33. Lippman, S.M., Kavanagh, J.J., Paredes-Espinoza, M., Delgadillo-Madrueno, F., Paredes-Casillas, P., Hong, W.K., Holdener, E., and Karakoff, 20 I.H. 13-cis-retinoic acid plus interferon alpha-2a: highly active systemic therapy for squamous cell carcinoma of the cervix. *Reports*, 84: 241-245, 1992.

34. Motzer, R.J., Schwartz, P., Murray Law, T., Hoffman, A.D., Albino, A.P., Vlamis, V., and Nanus, D.M. Antitumor effects of interferon alfa-2a and 13 cis-retinoic acid in renal cell carcinoma: Results of a phase II trial and in vitro studies. *J Clin Oncol*, 13: 1950-1957, 1995.
- 5 35. Berg, W.J., Schwartz, L.H., Amsterdam, A., Mazumdar, M., Murray-Law, T., Vlamis, V., Nanus, D.M., and Motzer, R.J. Clinical studies with 13-cis-retinoic acid in patients with advanced renal cell carcinoma. *Invest. New Drugs* 15(4):353-5 (1997).
- 10 36. Buer, J., Probst, M., Ganser, A., and Atzpodien, J. Response to 13-cis-retinoic acid plus interferon alfa-2a in two patients with therapy-refractory advanced renal cell carcinoma [letter]. *Journal of Clinical Oncology*, 13: 2679-2680, 1995.
- 15 37. Atzpodien, J., Kirchner, H., Duensing, S., Lopez Hanninen, E., Franzke, A., Buer, J., Probst, M., Anton, P., and Poliwoda, H. Biochemotherapy of advanced metastatic renal-cell carcinoma: results of the combination of interleukin-2, alpha-interferon, 5-fluorouracil, vinblastine, and 13-cis-retinoic acid. *World Journal of Urology*, 13: 174-177, 1995.
- 20 38. Bonhomme-faivre, L., Paule, B., Urien, S., Rudant, E., Bottius, L., Pradel, D., Marrot, D., All-trans retinoic acid, Hplc assay, Interferon alpha 2a, Pharmacokinetics, and Renal cell cancer pharmacokinetics of all-trans retinoic acid (ATAR) in patients with renal cancer concomitantly treated with interferon alpha 2a (IFN). *International Journal of Pharmaceutics*, 134: 99-104, 1996.

All references cited are incorporated herein by reference.

The compositions of this invention possess valuable pharmacological properties. They inhibit neoplasm cell proliferation and or angiogenesis in cancer therapy in human and veterinary medicine. Administration is
5 contemplated to include chronic, acute or intermittent regimens.

The compositions are particularly useful in treating renal cancers and other solid tumors.

In addition, the compositions can be used in in vitro methodologies, including diagnostics or screening procedures (e.g., in an assay sensitive
10 cancer types). In some embodiments, tissues, cells or material treated in vitro or extra corporeally will, thereafter, be reintroduced into a subject (which need not be the source of origin of the tissue, cells or material). Compounds of the present invention can be employed in admixture with carriers, excipients and other drugs, and radiation therapy.

15 The compositions of this invention are generally administered to animals, including but not limited to mammals such as livestock, household pets, humans, cattle, cats, dogs, poultry, etc.

The pharmacologically active compositions of this invention can be processed in accordance with conventional methods of Galenic pharmacy to
20 produce medicinal agents for administration to patients, e.g., mammals including humans.

The compositions of this invention can be employed in admixture with conventional excipients, i.e., pharmaceutically acceptable organic or

inorganic carrier substances suitable for parenteral, enteral (e.g., oral or inhalation) or topical application which do not deleteriously react with the active compositions. Suitable pharmaceutically acceptable carriers include but are not limited to water, salt solutions, etc. The pharmaceutical preparations can be sterilized and if desired mixed with auxiliary agents, e.g. They can also be combined where desired with other active agents, including radiation or other antineoplastic therapy.

In some embodiments of the present invention, dosage forms include instructions for the use of such compositions.

For parenteral application, particularly suitable are injectable, sterile solutions, preferably suspensions. Ampules are convenient unit dosages.

Sustained or directed release compositions can be formulated, e.g., liposomes or those wherein the active component is protected with differentially degradable coatings, e.g., by microencapsulation, multiple coatings, etc. It is also possible to freeze-dry the new compositions and use the lyophilizates obtained, for example, for the preparation of products for injection.

Generally, the two compositions of this invention are dispensed in unit dosage form comprising liposomal ATRA of from 15 to 300 or more mg/m² and particularly about 90 mg/m² ATRA. Interferon is administered at from about 1,000,000 to about 25,000,000 IU, and particularly from about 3,000,00 to about 5,000,000 sc and from daily to about 5 out of 7 days to about 3 out of 7 days per week.

It will be appreciated that the actual preferred amounts of active compositions in a specific case will vary according to the specific compositions being utilized, the particular compositions formulated, the mode of application, and the particular situs and organism being treated.

- 5 Dosages for a given host can be determined using conventional considerations, e.g., by customary comparison of the differential activities of the subject compositions and of a known agent, e.g., by means of an appropriate, conventional pharmacological protocol.

10.

11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65
66
67
68
69
70
71
72
73
74
75
76
77
78
79
80
81
82
83
84
85
86
87
88
89
90
91
92
93
94
95
96
97
98
99
100
101
102
103
104
105
106
107
108
109
110
111
112
113
114
115
116
117
118
119
120
121
122
123
124
125
126
127
128
129
130
131
132
133
134
135
136
137
138
139
140
141
142
143
144
145
146
147
148
149
150
151
152
153
154
155
156
157
158
159
160
161
162
163
164
165
166
167
168
169
170
171
172
173
174
175
176
177
178
179
180
181
182
183
184
185
186
187
188
189
190
191
192
193
194
195
196
197
198
199
200
201
202
203
204
205
206
207
208
209
210
211
212
213
214
215
216
217
218
219
220
221
222
223
224
225
226
227
228
229
230
231
232
233
234
235
236
237
238
239
240
241
242
243
244
245
246
247
248
249
250
251
252
253
254
255
256
257
258
259
260
261
262
263
264
265
266
267
268
269
270
271
272
273
274
275
276
277
278
279
280
281
282
283
284
285
286
287
288
289
290
291
292
293
294
295
296
297
298
299
300
301
302
303
304
305
306
307
308
309
310
311
312
313
314
315
316
317
318
319
320
321
322
323
324
325
326
327
328
329
330
331
332
333
334
335
336
337
338
339
340
341
342
343
344
345
346
347
348
349
350
351
352
353
354
355
356
357
358
359
360
361
362
363
364
365
366
367
368
369
370
371
372
373
374
375
376
377
378
379
380
381
382
383
384
385
386
387
388
389
390
391
392
393
394
395
396
397
398
399
400
401
402
403
404
405
406
407
408
409
410
411
412
413
414
415
416
417
418
419
420
421
422
423
424
425
426
427
428
429
430
431
432
433
434
435
436
437
438
439
440
441
442
443
444
445
446
447
448
449
450
451
452
453
454
455
456
457
458
459
460
461
462
463
464
465
466
467
468
469
470
471
472
473
474
475
476
477
478
479
480
481
482
483
484
485
486
487
488
489
490
491
492
493
494
495
496
497
498
499
500
501
502
503
504
505
506
507
508
509
510
511
512
513
514
515
516
517
518
519
520
521
522
523
524
525
526
527
528
529
530
531
532
533
534
535
536
537
538
539
540
541
542
543
544
545
546
547
548
549
550
551
552
553
554
555
556
557
558
559
560
561
562
563
564
565
566
567
568
569
570
571
572
573
574
575
576
577
578
579
580
581
582
583
584
585
586
587
588
589
590
591
592
593
594
595
596
597
598
599
600
601
602
603
604
605
606
607
608
609
610
611
612
613
614
615
616
617
618
619
620
621
622
623
624
625
626
627
628
629
630
631
632
633
634
635
636
637
638
639
640
641
642
643
644
645
646
647
648
649
650
651
652
653
654
655
656
657
658
659
660
661
662
663
664
665
666
667
668
669
670
671
672
673
674
675
676
677
678
679
680
681
682
683
684
685
686
687
688
689
690
691
692
693
694
695
696
697
698
699
700
701
702
703
704
705
706
707
708
709
710
711
712
713
714
715
716
717
718
719
720
721
722
723
724
725
726
727
728
729
730
731
732
733
734
735
736
737
738
739
740
741
742
743
744
745
746
747
748
749
750
751
752
753
754
755
756
757
758
759
760
761
762
763
764
765
766
767
768
769
770
771
772
773
774
775
776
777
778
779
780
781
782
783
784
785
786
787
788
789
790
791
792
793
794
795
796
797
798
799
800
801
802
803
804
805
806
807
808
809
810
811
812
813
814
815
816
817
818
819
820
821
822
823
824
825
826
827
828
829
830
831
832
833
834
835
836
837
838
839
840
841
842
843
844
845
846
847
848
849
850
851
852
853
854
855
856
857
858
859
860
861
862
863
864
865
866
867
868
869
870
871
872
873
874
875
876
877
878
879
880
881
882
883
884
885
886
887
888
889
890
891
892
893
894
895
896
897
898
899
900
901
902
903
904
905
906
907
908
909
910
911
912
913
914
915
916
917
918
919
920
921
922
923
924
925
926
927
928
929
930
931
932
933
934
935
936
937
938
939
940
941
942
943
944
945
946
947
948
949
950
951
952
953
954
955
956
957
958
959
960
961
962
963
964
965
966
967
968
969
970
971
972
973
974
975
976
977
978
979
980
981
982
983
984
985
986
987
988
989
990
991
992
993
994
995
996
997
998
999
1000
1001
1002
1003
1004
1005
1006
1007
1008
1009
1010
1011
1012
1013
1014
1015
1016
1017
1018
1019
1020
1021
1022
1023
1024
1025
1026
1027
1028
1029
1030
1031
1032
1033
1034
1035
1036
1037
1038
1039
1040
1041
1042
1043
1044
1045
1046
1047
1048
1049
1050
1051
1052
1053
1054
1055
1056
1057
1058
1059
1060
1061
1062
1063
1064
1065
1066
1067
1068
1069
1070
1071
1072
1073
1074
1075
1076
1077
1078
1079
1080
1081
1082
1083
1084
1085
1086
1087
1088
1089
1090
1091
1092
1093
1094
1095
1096
1097
1098
1099
1100
1101
1102
1103
1104
1105
1106
1107
1108
1109
1110
1111
1112
1113
1114
1115
1116
1117
1118
1119
1120
1121
1122
1123
1124
1125
1126
1127
1128
1129
1130
1131
1132
1133
1134
1135
1136
1137
1138
1139
1140
1141
1142
1143
1144
1145
1146
1147
1148
1149
1150
1151
1152
1153
1154
1155
1156
1157
1158
1159
1160
1161
1162
1163
1164
1165
1166
1167
1168
1169
1170
1171
1172
1173
1174
1175
1176
1177
1178
1179
1180
1181
1182
1183
1184
1185
1186
1187
1188
1189
1190
1191
1192
1193
1194
1195
1196
1197
1198
1199
1200
1201
1202
1203
1204
1205
1206
1207
1208
1209
1210
1211
1212
1213
1214
1215
1216
1217
1218
1219
1220
1221
1222
1223
1224
1225
1226
1227
1228
1229
1230
1231
1232
1233
1234
1235
1236
1237
1238
1239
1240
1241
1242
1243
1244
1245
1246
1247
1248
1249
1250
1251
1252
1253
1254
1255
1256
1257
1258
1259
1260
1261
1262
1263
1264
1265
1266
1267
1268
1269
1270
1271
1272
1273
1274
1275
1276
1277
1278
1279
1280
1281
1282
1283
1284
1285
1286
1287
1288
1289
1290
1291
1292
1293
1294
1295
1296
1297
1298
1299
1300
1301
1302
1303
1304
1305
1306
1307
1308
1309
1310
1311
1312
1313
1314
1315
1316
1317
1318
1319
1320
1321
1322
1323
1324
1325
1326
1327
1328
1329
1330
1331
1332
1333
1334
1335
1336
1337
1338
1339
1340
1341
1342
1343
1344
1345
1346
1347
1348
1349
1350
1351
1352
1353
1354
1355
1356
1357
1358
1359
1360
1361
1362
1363
1364
1365
1366
1367
1368
1369
1370
1371
1372
1373
1374
1375
1376
1377
1378
1379
1380
1381
1382
1383
1384
1385
1386
1387
1388
1389
1390
1391
1392
1393
1394
1395
1396
1397
1398
1399
1400
1401
1402
1403
1404
1405
1406
1407
1408
1409
1410
1411
1412
1413
1414
1415
1416
1417
1418
1419
1420
1421
1422
1423
1424
1425
1426
1427
1428
1429
1430
1431
1432
1433
1434
1435
1436
1437
1438
1439
1440
1441
1442
1443
1444
1445
1446
1447
1448
1449
1450
1451
1452
1453
1454
1455
1456
1457
1458
1459
1460
1461
1462
1463
1464
1465
1466
1467
1468
1469
1470
1471
1472
1473
1474
1475
1476
1477
1478
1479
1480
1481
1482
1483
1484
1485
1486
1487
1488
1489
1490
1491
1492
1493
1494
1495
1496
1497
1498
1499
1500
1501
1502
1503
1504
1505
1506
1507
1508
1509
1510
1511
1512
1513
1514
1515
1516
1517
1518
1519
1520
1521
1522
1523
1524
1525
1526
1527
1528
1529
1530
1531
1532
1533
1534
1535
1536
1537
1538
1539
1540
1541
1542
1543
1544
1545
1546
1547
1548
1549
1550
1551
1552
1553
1554
1555
1556
1557
1558
1559
1560
1561
1562
1563
1564
1565
1566
1567
1568
1569
1570
1571
1572
1573
1574
1575
1576
1577
1578
1579
1580
1581
1582
1583
1584
1585
1586
1587
1588
1589
1590
1591
1592
1593
1594
1595
1596
1597
1598
1599
1600
1601
1602
1603
1604
1605
1606
1607
1608
1609
1610
1611
1612
1613
1614
1615
1616
1617
1618
1619
1620
1621
1622
1623
1624
1625
1626
1627
1628
1629
1630
1631
1632
1633
1634
1635
1636
1637
1638
1639
1640
1641
1642
1643
1644
1645
1646
1647
1648
1649
1650
1651
1652
1653
1654
1655
1656
1657
1658
1659
1660
1661
1662
1663
1664
1665
1666
1667
1668
1669
1670
1671
1672
1673
1674
1675
1676
1677
1678
1679
1680
1681
1682
1683
1684
1685
1686
1687
1688
1689
1690
1691
1692
1693
1694
1695
1696
1697
1698
1699
1700
1701
1702
1703
1704
1705
1706
1707
1708
1709
1710
1711
1712
1713
1714
1715
1716
1717
1718
1719
1720
1721
1722
1723
1724
1725
1726
1727
1728
1729
1730
1731
1732
1733
1734
1735
1736
1737
1738
1739
1740
1741
1742
1743
1744
1745
1746
1747
1748
1749
1750
1751
1752
1753
1754
1755
1756
1757
1758
1759
1760
1761
1762
1763
1764
1765
1766
1767
1768
1769
1770
1771
1772
1773
1774
1775
1776
1777
1778
1779
1780
1781
1782
1783
1784
1785
1786
1787
1788
1789
1790
1791
1792
1793
1794
1795
1796
1797
1798
1799
1800
1801
1802
1803
1804
1805
1806
1807
1808
1809
1810
1811
1812
1813
1814
1815
1816
1817
1818
1819
1820
1821
1822
1823
1824
1825
1826
1827
1828
1829
1830
1831
1832
1833
1834
1835
1836
1837
1838
1839
1840
1841
1842
1843
1844
1845
1846
1847
1848
1849
1850
1851
1852
1853
1854
1855
1856
1857
1858
1859
1860
1861
1862
1863
1864
1865
1866
1867
1868
1869
1870
1871
1872
1873
1874
1875
1876
1877
1878
1879
1880
1881
1882
1883
1884
1885
1886
1887
1888
1889
1890
1891
1892
1893
1894
1895
1896
1897
1898
1899
1900
1901
1902
1903
1904
1905
1906
1907
1908
1909
1910
1911
1912
1913
1914
1915
1916
1917
1918
1919
1920
1921
1922
1923
1924
1925
1926
1927
1928
1929
1930
1931
1932
1933
1934
1935
1936
1937
1938
1939
1940
1941
1942
1943
1944
1945
1946
1947
1948
1949
1950
1951
1952
1953
1954
1955
1956
1957
1958
1959
1960
1961
1962
1963
1964
1965
1966
1967
1968
1969
1970
1971
1972
1973
1974
1975
1976
1977
1978
1979
1980
1981
1982
1983
1984
1985
1986
1987
1988
1989
1990
1991
1992
1993
1994
1995
1996
1997
1998
1999
2000
2001
2002
2003
2004
2005
2006
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
2018
2019
2020
2021
2022
2023
2024
2025
2026
2027
2028
2029
2030
2031
2032
2033
2034
2035
2036
2037
2038
2039
2040
2041
2042
2043
2044
2045
2046
2047
2048
2049
2050
2051
2052
2053
2054
2055
2056
2057
2058
2059
2060
2061
2062
2063
2064
2065
2066
2067
2068
2069
2070
2071
2072
2073
2074
2075
2076
2077
2078
2079
2080
2081
2082
2083
2084
2085
2086
2087
2088
2089
2090
2091
2092
2093
2094
2095
2096
2097
2098
2099
2100
2101
2102
2103
2104
2105
2106
2107
2108
2109
2110
2111
2112
2113
2114
2115
2116
2117
2118
2119
2120
2121
2122
2123
2124
2125
2126
2127
2128
2129
2130
2131
2132
2133
2134
2135
2136
2137
2138
2139
2140
2141
2142
2143
2144
2145
2146
2147
2148
2149
2150
2151
2152
2153
2154
2155
2156
2157
2158
2159
2160
2161
2162
2163
2164
2165
2166
2167
2168
2169
2170
2171
2172
2173
2174
2175
2176
2177
2178
2179
2180
2181
2182
2183
2184
2185
2186
2187
2188
2189
2190
2191
2192
2193
2194
2195
2196
2197
2198
2199
2200
2201
2202
2203
2204
2205
2206
2207
2208
2209
2210